

Clinicopathologic features of hepatic neoplasms in explanted livers: a single institution experience

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BACKGROUND: Hepatic neoplasms can be the primary indication for hepatic transplantation. The tumors can also be incidentally identified in explanted livers. We explored the clinicopathologic features of hepatic neoplasms identified in explanted livers.

MATERIALS AND METHODS: All explanted livers resected between 2001 and 2006 were evaluated for the presence of neoplasms and their clinicopathologic features were examined.

RESULTS: In 98 liver transplants, 15 neoplasms (15.3%) were identified. Patient ages ranged from 5 to 63 years (median, 56 years). The primary etiology of hepatic disease was hepatitis C virus in 12 cases, hepatitis B virus in 1 case, cryptogenic cirrhosis in 1 case and congenital hepatic fibrosis in 1 case. Serum alpha-fetoprotein was significantly elevated (>400 U/L) in only 2 cases. CA19-9 was not elevated in any of the cases. The tumors included hepatocellular carcinoma (HCC) in 13 cases, 1 case of cholangiocarcinoma and 1 case of combined HCC and hepatoblastoma. The tumors ranged in size from 0.5 to 5 cm (median 1.4 cm) and were multifocal in 5 of the cases (33%). Tissue alpha-fetoprotein expression was only seen in the cases associated with elevated serum levels.

CONCLUSION: In our institution hepatic neoplasms are seen in more than 15% of explanted livers. They can be incidentally identified, are frequently not associated with elevated serum levels of alpha-fetoprotein and CA19-9, are commonly multifocal but small, and are associated with good prognosis. Elevated serum alpha-fetoprotein, albeit specific, is not a very sensitive marker in the detection of hepatic neoplasms.

The presence of a hepatic neoplasm is one of the indications for hepatic transplantation. Currently less than 10% of hepatic transplantation is performed for hepatic malignancy.¹ Patients with hepatic neoplasms fulfilling the Milan criteria are good candidates for hepatic transplantation.² Hepatic neoplasms can be incidentally identified in explanted livers without the pre-operative suspicion of the presence of a neoplasm.^{3,4,5} One other indication for hepatic transplantation is markedly increased levels of serum alpha-fetoprotein in patients with end-stage hepatic disease waiting for transplantation.⁶ The prognosis of hepatic transplantation for hepatic neoplasms depends, in large part, on certain clinicopathologic parameters. These include tumor size, grade, vascular invasion and the general clinical condition of the patient.^{7,8,9} In this

study we attempted to analyze clinicopathologic parameters of hepatic neoplasms identified in explanted livers in our institution to see if we could identify features that would help us more properly manage patients with end-stage liver disease preparing for transplantation.

MATERIALS AND METHODS

All explanted livers resected for hepatic transplantation at King Faisal Specialist Hospital and Research Center between the years 2001 and 2006 were reviewed. Cases with the diagnosis of a hepatic neoplasm were selected. The slides and reports pertaining to the resected liver were reviewed. The tumors were histologically evaluated by three pathologists (WAM, MAO and HA). The tumor size was obtained from the gross pathology report and the tumors were classified and graded

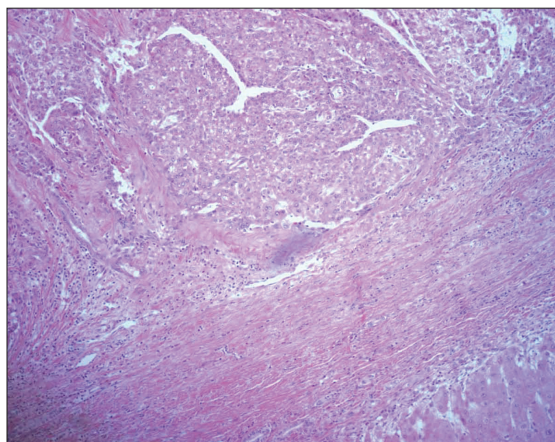


Figure 1a. Case of grade 1 hepatocellular carcinoma (top) with a thick capsule and adjacent reactive hepatic tissue (bottom). Serum alpha-fetoprotein was slightly increased and tissue alphafetoprotein was negative (H&E stain X100).

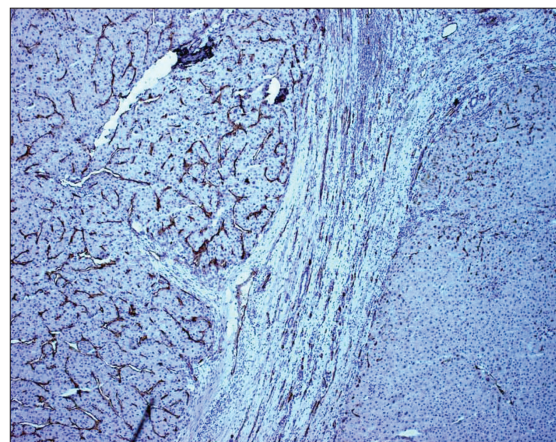


Figure 1b. Same case as Figure 1a of grade 1 hepatocellular carcinoma showing CD34 expression in the tumor nodule (left) with lack of expression in the reactive liver (right) (immunoperoxidase X50).

according to the Edmondson grading system for hepatocellular carcinoma.¹⁰ Immunohistochemical stains for alpha-fetoprotein and CA19-9 were performed in all cases. CD34 immunostaining was performed for low-grade neoplasm to highlight the vascular pattern of the neoplasms. Patient charts were reviewed. The clinical data pertaining to age, sex and primary hepatic disease were tabulated. Laboratory findings related to serum levels of alpha-fetoprotein and serum CA19-9 pre- and post-transplantation were also obtained from patient charts. Clinical status related to patient condition in relation to survival, recurrence of tumor and serum levels of alpha-fetoprotein and CA19-9 at last follow up were also recorded.

RESULTS

There were 98 hepatic transplantations performed in our institution between the years 2001 and 2006 and 15 neoplasms, representing 15.3% of all transplants, were identified. Patient ages ranged from 5 to 63 years (median, 56 years). There was only one child among the group of transplanted patients that had a hepatic neoplasm. The primary underlying indication for transplantation was hepatitis C in 12 cases (80%), hepatitis B in one case, cryptogenic hepatitis in one case and congenital hepatic fibrosis in one case.

Serum alpha-fetoprotein was significantly elevated (>400 U/L) in only two patients (6.6%). One patient had serum alpha-fetoprotein of 10 000 U/L and the other had a level of 700 U/L. None of the patients had an elevated level of serum CA19-9.

Clinical and radiologic suspicion of the presence of neoplasm was present in 13 of the patients. Two

patients had no preoperative clinical suspicion for the presence of neoplasm.

Of the 15 tumors identified, hepatocellular carcinoma was seen in 13 cases (86.6%). There was one case of cholangiocarcinoma and one case of combined hepatocellular carcinoma and hepatoblastoma. The tumor grade was Edmonson grade 1 in two cases, grade 2 in 11 cases and grade 3 in one case. The two low-grade tumors required the use of CD34 immunostain to highlight the vascular pattern of the neoplastic nodule in comparison to the diseased liver (Figure 1a, b). Only two cases showed expression of alpha-fetoprotein in the neoplasm including a case of hepatoblastoma and high-grade hepatocellular carcinoma (Figure 2a, b). This corresponded to the two cases showing elevated serum levels.

The 15 tumors ranged in size from 0.5 cm to 5.0 cm in greatest diameter with a median diameter of 1.4 cm. The tumors were multifocal and microscopic in five of the cases (33%). Four tumors (26.6%) were missed on initial pathologic examination and identified upon pathological re-examination of the explanted liver at the request of the transplantation surgeon.

The only pediatric patient in our series was an 8-year-old female with a history of congenital hepatic fibrosis. She presented with markedly elevated serum alpha-fetoprotein (10 000 U/L). No evidence of a neoplasm was clinically or radiologically suspected. After the liver was explanted a critical review of the CT scan of the liver showed focal hypodense hepatic lesions in segment #7 (Figure 3). She received a living-related liver transplantation. Examination of the liver showed end-stage hepatic cirrhosis with multiple microscopic foci of

hepatocellular carcinoma and hepatoblastoma (Figure 4a, b). Several weeks post-operatively the serum levels of alphafetoprotein returned to normal. The patient was free of disease one year after transplantation.

Follow-up information ranging from 4 to 48 months was available on all patients with a median follow up period of 20 months. Two patients died of primary graft failure and all other patients are alive with no evidence of recurrence or residual disease.

DISCUSSION

Hepatocellular carcinoma shows tissue expression of alpha-fetoprotein in 20% to 40% of cases.¹⁰ Tissue expression in our series was seen in only 13.3% of the cases. It has been shown that tissue expression of alpha-fetoprotein corresponds to high serum levels and high-grade tumors.¹¹ This finding was confirmed in our series where tissue expression corresponded to serum levels of alpha-fetoprotein. The only two cases that showed tissue expression of alphafetoprotein had elevated serum levels. The cases were high-grade hepatocellular carcinoma and hepatoblastoma. This finding suggests that most hepatocellular carcinomas do not express alpha-fetoprotein either at the tissue level or at the secretory level. This indicates the low sensitivity of the test and suggests the need for a more sensitive test for early detection of hepatocellular carcinoma.

The rate of incidentally identified neoplasm in explanted livers ranges from 10% to 50% of the cases depending on the study.^{3,12} This rate depends on how closely patients with end-stage hepatic disease are followed. The rate is low in developing countries and higher in developed ones. We found incidental neoplasms in 13% of our series. Four cases required repeated gross inspection of the explanted liver to identify the neoplasm upon request of the transplant surgeon. This was mainly due to the small size of the tumors. The tumors were also well differentiated in many incidents requiring the use of immunohistochemistry to differentiate the nodules from the cirrhotic reparative nodules. It therefore appears that it is extremely important to thoroughly examine explanted livers to identify small multifocal neoplasms.

Tumor size and grade are two of the most significant prognostic indicators in hepatocellular carcinoma. In one study, large tumor size and high tumor grade could predict vascular invasion and a poor outcome.¹³ Another study showed that tumor size together with Ki-67 proliferation index and p53 expression are the most significant prognostic indicators. None of our patients succumbed to their diseases. This may be mainly explained by the predominantly small size of the primary tumors

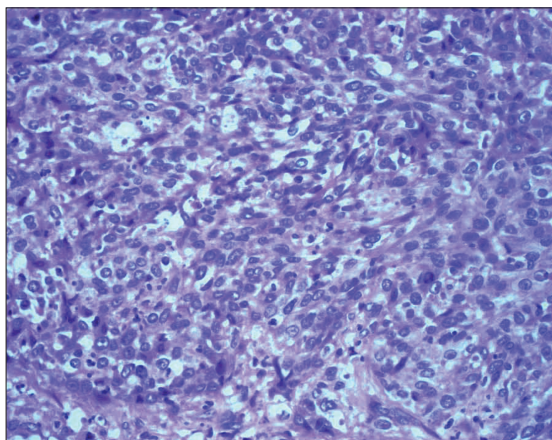


Figure 2a. Case of grade 3 hepatocellular carcinoma with focal sarcomatoid changes (H & E X400).

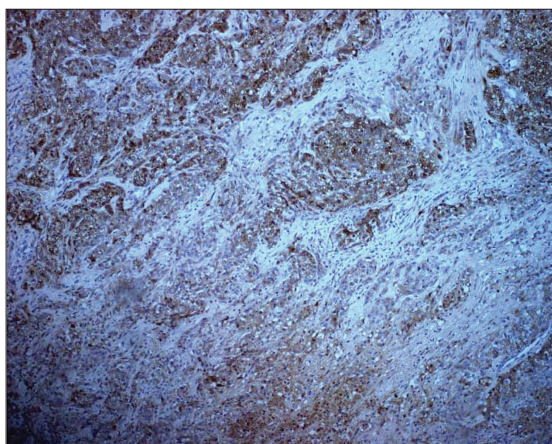


Figure 2b. Same case as Figure 2a showing strong expression of alpha-fetoprotein. Serum alpha-fetoprotein was 700 U/L (Immunoperoxidase X200).

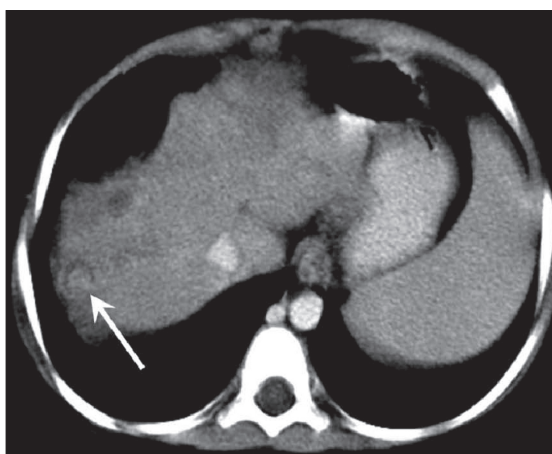


Figure 3. Transverse contrast enhanced CT demonstrated focal hypodense hepatic lesion in segment #7 with focal central enhancement (nodule-in-nodule) represents hepatocellular carcinoma within a dysplastic nodule (arrow).

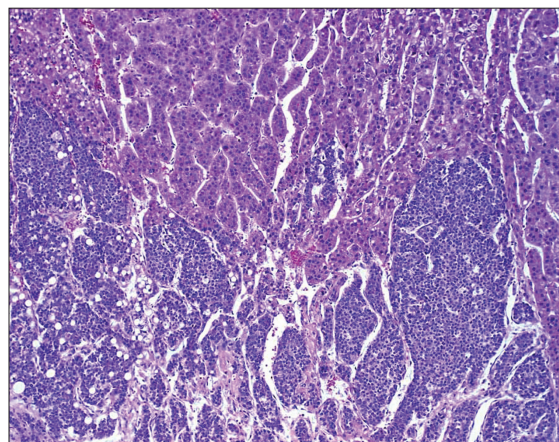


Figure 4a. Case of combined hepatocellular carcinoma (top) and hepatoblastoma (bottom) in an 8-year-old female (H&E X200).

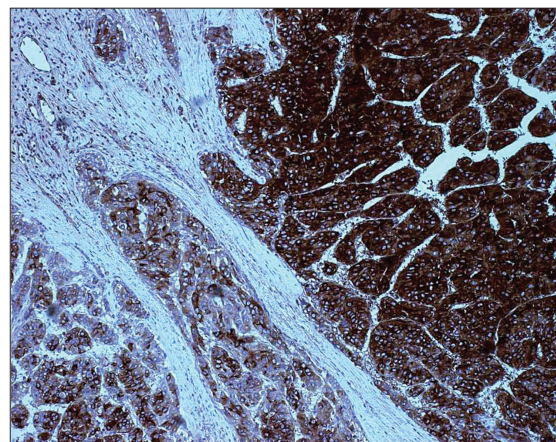


Figure 4b. Case of combined hepatocellular carcinoma and hepatoblastoma showing strong expression of alpha-fetoprotein. The patient serum level of alpha-fetoprotein was 10000 U/L (Immunoperoxidase X200).

and the prevalence of low grade. Malignant neoplasms are one of the indications for hepatic transplantation.¹ Patients with chronic end-stage hepatic disease who develop clinical or radiographic evidence of a neoplasm are candidates for hepatic transplantation, especially if the tumor is resectable with no evidence of metastasis. This is especially true when the tumor is associated with marked elevation of serum alpha-fetoprotein.

Serum levels of alpha-fetoprotein have been shown to be markedly elevated in more than 60% of cases of hepatocellular carcinoma.^{6,10} Levels above 400 U/L have been suggested as a surrogate test for the presence of a neoplasm.¹⁶ Although high levels have been seen in non-neoplastic conditions of the liver such as hepatitis C, this occurrence is not very frequent.¹⁵ These levels would, however, rarely reach levels associated with neoplasms (>400 U/L). In our series, we did not see a high incidence of elevated serum alpha-fetoprotein. Less than 20% of our cases were associated with markedly elevated levels of serum alpha-fetoprotein. Extremely high levels of serum alpha-fetoprotein have been linked

with poor prognostic indicators such as large tumors, vascular invasion and poor survival.¹⁶ Our patients had smaller tumors and better survival.

Paradoxically, one of our patients had extremely high levels of alpha-fetoprotein without any clinical or radiographic evidence of a neoplasm. The resected liver showed multiple microscopic foci of hepatocellular carcinoma and hepatoblastoma. This may indicate that extremely high levels of alpha-fetoprotein may be seen in the absence of clinically or radiologically detectable tumor. This also suggests the level of serum expression of alpha-fetoprotein may be related to individual cell expression of the protein usually seen in high grade neoplasms and hepatoblastoma rather than being related to tumor size or vascular invasion. It thus seems that markedly elevated levels of serum-alpha-fetoprotein in patients with long-standing chronic liver disease with failure may be suggestive of a hepatic neoplasm and an indication for hepatic transplantation even in the absence of a clinically or radiologically detectable tumor.

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